UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

JUN 27 1997

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Alachlor (4th)

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The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on February 05, 1997 to discuss and evaluate the weight-of-the-evidence on alachlor with particular reference to its carcinogenic potential and to consider the comments from the FIFRA Scientific Advisory Panel (SAP).

In accordance with the EPA proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996), alachlor was characterized as "likely" to be a human carcinogen at high doses, but "not likely" at low doses, by all routes of exposure. This conclusion was based on increased incidences of malignant and combined benign/malignant multiple tumor types in both sexes of the Long Evans rat, which occurred mainly at higher doses. Based on a consideration of modes of action for these tumors, the CPRC agreed that a non-linear margin of exposure (MOE) approach should be used for the purpose of risk assessment. The consensus of the CPRC was that MOEs for both the malignant mixed gastric tumors and the nasal adenomas be presented for a risk management decision.

SUMMARY

Alachlor was previously classified as a Group B2 - probable human carcinogen - by the Toxicology Peer Review Committee at the first and second Peer Reviews (1986 and 1987, respectively). At the third Peer Review of Alachlor (1996), classification was deferred pending promulgation of the new Guidelines for Carcinogenic Risk Assessment.

On October 30, 1996 the SAP met to consider the weight-of-evidence for alachlor. The SAP was asked to comment on mode of action data, provided by the registrant, for the tumor types in the rat associated with administration of alachlor. At the present Peer Review meeting (fourth), the CPRC considered the animal data and supporting information, along with the recommendations of the SAP regarding the mode of action data [a detailed discussion can be found in section D.]:

A summary of the animal data for alachlor follows:

Administration of alachlor in the diet to Long-Evans rats at doses up to 126 mg/kg/day resulted in:

In males: statistically significant increases in thyroid follicular cell adenomas, carcinomas and combined adenoma/carcinoma; stomach osteosarcomas, malignant mixed gastric tumors and combined gastric adenocarcinomas/malignant mixed gastric tumors; nasal respiratory epithelial adenomas and combined adenoma/adenocarcinoma. The increases in thyroid and gastric tumors were significant at the highest dose tested (HDT), 126 mg/kg/day; the increase in nasal tumors was significant at both 42 and 126 mg/kg/day. There were also statistically significant positive trends for all the tumors, as well as for stomach gastric adenocarcinomas.

In females: statistically significant increases in stomach malignant mixed gastric tumors, combined gastric adenocarcinomas/ malignant mixed gastric tumors and nasal respiratory epithelial adenomas and combined adenoma/adenocarcinoma. The increases in gastric tumors was significant at the HDT, 126 mg/kg/day; the increase in nasal tumors was significant at both 42 and 126 mg/kg/day. There were also statistically significant positive trends for all the tumors as well as for thyroid follicular cell adenocarcinomas and adenoma/adenocarcinoma combined.

In a second study in Long-Evans rats, administration of alachlor in the diet at doses up to 15 mg/kg/day resulted in a statistically significant increase in the incidence of nasal respiratory epithelial adenomas at the HDT, with a statistically significant positive trend in both sexes. In female rats there was also a statistically significant increase in thymus malignant lymphosarcomas at the HDT.

Administration of alachlor in the diet to CD-1 mice (1981) at doses up to 260 mg/kg/day resulted in statistically significant increases in bronchioalveolar adenomas and combined adenoma/carcinoma at the HDT only *in female mice* with a statistically significant positive trend. In male mice there was only a statistically significant positive trend for bronchioalveolar adenomas.

In a second carcinogenicity study in CD-1 mice (1994) administration of alachlor in the diet at doses up to 262.4 mg/kg/day resulted in a statistically significant increase in the incidence of bronchioalveolar adenomas and combined adenoma/carcinoma at all doses *in male mice*. No compound-related increases in female mice were reported.

Alachlor is structurally related to acetochlor, butachlor, metolachlor and SAN 582H, which are all associated with carcinogenic responses in rodents.

Alachlor also induces unscheduled DNA syntheses (UDS) in vivo at 1000 mg/kg in rats and a few of its metabolites are weakly genotoxic in the Salmonellla assay. Alachlor, as well as several of its structurally related analogs, was consistently clastogenic in in vitro systems; however, with few exceptions, clastogenic activity was not observed in vivo.

The SAP and CPRC conclusions on the tumors induced by alachlor in the rat are summarized as follows:

Thyroid tumors: Both the SAP and the CPRC agreed that the Agency requirements for demonstrating a hormonal mode of action were met by the registrant and that the tumors were observed only at an excessive dose.

Stomach: The SAP stated: "Evidence was presented that the carcinomas resulting from alachlor were examined to prove that they were carcinoids, not adenocarcinomas or gastric sarcomas, which are unrelated to the proposed gastrin-induced effect". The CPRC felt that the evidence alluded to was based on the butachlor study and that the tumors in the alachlor study could be assumed to be carcinoids, by inference only. Although the tumor increases were significant only at the highest dose (excessive), it was noted that there was also 1 tumor (vs 0 in controls) at the mid-dose (which was considered to be adequate, not excessive) and this is a rare tumor type.

Nasal tumors: The SAP considered these possibly relevant to humans but only at exposures in excess of anticipated human exposures for pesticide use. The CPRC considered these tumors relevant to humans (with a quantitative difference). There also was 1 tumor at the mid-dose (not excessive) and this too is a rare tumor type.

A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William Burnam

Karl Baetcke

Marion Copley

Kerry Dearfield

Yiannakis Ioannou

Hugh Pettigrew

Esther Rinde

Yin Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Stephen Dapson[1]

Timothy McMahon

Jess Rowland

Lori Brunsman

Lucas Brennecke[2] (PAI/ORNL) SEE 4a

3. Other Attendees: Bernice Fisher, Nancy McCarroll, Paula Deschamp (HED).

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

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B. Material Reviewed

The material available for review consisted of DERs, one-liners, data from the literature and other data summaries (including comments from the FIFRA Scientific Advisory Panel) prepared and/or supplied by Drs. Dapson and McMahon, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information:

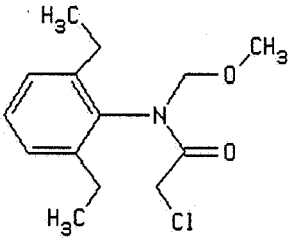

Figure 2

Alachlor

Synonyms: (2-chloro-2'6'-diethyl-N-(methoxymethyl)-acetanilide), $C_{14}H_{20}NO_2Cl$, Alanex®, CP 50144®, Lasso®, Lazo, CAS# 15972-60-8, EPA Pesticide Chemical Code 090501.

Alachlor is a chloroacetanilide herbicide. It is registered for use as a selective preemergence herbicide for the control of many preemergent broadleaf weeds and grasses on corn (all types), soybeans, peanuts, dry beans, potatoes, cotton, and certain woody ornamentals. In December 1984, a Special Review Position Document 1 was issued on alachlor, in which the Agency concluded that alachlor is a Group B2 carcinogen based on the 1984 "proposed" EPA Guidelines (at that time), and that "the weight of the evidence demonstrates that alachlor is oncogenic to laboratory animals and, in the absence of data on humans, it is prudent to treat alachlor as a probable human carcinogen". A Special Review Position Document 2,3 was also prepared on alachlor.

Previous meetings of the Health Effects Division Carcinogenicity Peer Review Committee on Alachlor determined the following (on March 25, 1986 and April 15, 1987):

Alachlor met all but one of the criteria specified for the B2 classification any of which alone can be sufficient for such a classification. That is, alachlor produced an increased incidence in malignant, or combined malignant and benign, nasal turbinate tumors (and other tumor types) in Long-Evans rats in three different experiments at more than one dose level via dietary administration. Alachlor also produced a statistically significant increase in lung tumors in female CD-1 mice at 2 dose levels. In another experiment with Long-Evans rats, nasal turbinate tumors occurred after only 5-6 months of exposure. The tumor incidence was as high as 50% and the tumor site was unusual; i.e., not an increase of a normal high background tumor type. Additionally, a metabolite of alachlor was mutagenic in the Ames Test at 6 dose levels.

The Third Meeting of the Health Effects Division Carcinogenicity Peer Review Committee on Alachlor determined the following (held on September 27 and October 4, 1995 and January 3, 1996):

The weight-of-the-evidence for alachlor was re-evaluated with particular reference to its carcinogenic potential, based on mechanistic and other data provided by the registrant. These data were not requested by the Agency but were provided by the registrant in support of their chemical. The classification of alachlor at that time was a Group B2 - probable human carcinogen, with a recommendation that a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*).

New data provided by the registrant consisted of a new mouse carcinogenicity study, additional mutagenicity studies, mechanistic data, and additional metabolism studies and toxicology data from a related compound, butachlor. Upon evaluation of all of the submitted data regarding the carcinogenicity potential of alachlor and consideration of the full weight-of-the-evidence, the Health Effects Division Carcinogenicity Peer Review Committee could not reach a consensus as to the classification of alachlor as a carcinogen. Therefore the CPRC recommended to defer the carcinogenicity classification of alachlor and reconsider the classification at a later date, using the new Cancer Assessment Guidelines when such guidelines are in effect. In addition, the CPRC recommended not to utilize the linear low dose approach, but

to utilize the Margin of Exposure (MOE) methodology for the estimation of human risk. The CPRC concluded that the data in support of the mechanism for the nasal turbinates is indicative of a rat specific response. Although the rat and human were recognized to possess the same enzyme(s) involved in production of the putative toxic species from alachlor, it was also recognized that the activity of these enzymes was substantially greater in the rat compared to the human. Thus, the model of rat nasal tumorigenesis may not be relevant for human cancer assessment. Thyroid tumors have been proposed to be the result of induction of hepatic glucuronyl transferase with subsequent decrease in circulating T3 and T4, a subsequent increase in TSH, and eventual hyperplastic response of the thyroid. The mechanistic data for thyroid tumor formation meet the criteria established by the Agency and the use of the MOE approach for human cancer assessment is consistent with Agency policy. The CPRC stated that the stomach tumor formation was a direct contact effect, non-genotoxic mechanism which parallels human pathological conditions. These tumors result from an indirect response to change in pH. The use of the MOE approach for human cancer assessment was consistent with Agency policy.

D. Summary of Carcinogenicity and Mechanistic Data

1. Human Data

The interspecies biotransformation of alachlor as related to toxicity has been investigated in subcellular tissue fractions from rats and humans. In a study submitted to and reviewed by the Office of Pesticide Programs, cytosolic and microsomal fractions from rat and human liver and nasal tissues were studied to determine the differential species capability to conjugate alachlor with glutathione, to hydrolyze the secondary sulfide metabolite of alachlor, and to hydroxylate the 2,6-diethylaniline metabolite of alachlor. The velocity of the glutathione conjugation reaction in the rat liver and nasal tissue was 4.0 and 32.5 times greater than in human liver and nasal tissue, respectively. The velocity of hydrolysis of the secondary sulfide was 5.8 times greater in rat nasal tissue than in human. The velocity of hydroxylation of the diethylaniline metabolite of alachlor was 7.5 times greater in the rat liver compared to human, and 129.8 times greater in the rat nasal tissue compared to human. The results of this study suggest that the ability of human tissues to metabolize alachlor to the putative toxic metabolite diethylbenzoquinone imine is much less in comparison to the rat. The SAP concluded that because bioactivation is thought to play a key role in the mechanism for nasal tumor formation, the evidence that bioactivation in humans occurs at significantly lower rates than in rats should be compelling.

The SAP suggested that the analogy to the drug phenacetin is noteworthy. Its proposed toxic metabolite is also a benzoquinone imine and phenacetin produces nasal tumors in rats. However, in humans, carcinogenicity is observed in the lower urinary tract, and only at high doses. Thus, by analogy, although alachlor cannot be completely excluded from having activity in humans, it may only occur at doses in excess of anticipated human exposure levels for pesticide use.

In two published studies (American J Industrial Medicine 30: 300-306, 1996; Environ. Health Perspect. 104: 728-733, 1996) a cohort was investigated for mortality rates and cancer incidence from 1969 to 1993 in manufacturing workers with potential exposure to alachlor. Mortality from all causes combined in workers judged to have high alachlor exposure was decreased in relation to the standardized mortality ratio, while cancer mortality was similar to the standardized mortality ratio for this cause of death. There were no cancer deaths among workers with 5 or more years of high exposure, and 15 years since first exposure. In the earlier report, (American J Industrial Medicine 30: 300-306, 1996), the authors observed that alachlor-exposed workers had elevated rates of colo-

rectal cancer and that the excess occurred in male workers with 5 or more years in high alachlor exposure jobs. The major limitation of this study was the small size of the study population and minimal length of follow-up. The later report (Environ Health Perspect 104: 728-733, 1996) provided some additional follow-up that lessened the observed/expected ratio reported for colorectal cancer. While these findings suggested no appreciable effects of exposure to alachlor on worker mortality or cancer incidence, the authors suggested that further follow-up of those workers with high exposure to alachlor is important to monitor the incidence from colorectal and other cancers, since the cohort is still relatively young and the follow-up period relatively short. It is noted that none of the animal studies with alachlor demonstrated any increased incidence of colorectal cancer.

2. Animal Data

The potential carcinogenicity of alachlor has been extensively investigated in studies in both rats and mice. Studies in Long-Evans rats demonstrated increased incidence of nasal epithelial tumors, glandular stomach tumors, and thyroid follicular cell tumors. Studies in CD-1 mice showed evidence of bronchioalveolar adenoma and combined adenoma/carcinoma, but the data were considered to be inconclusive.

In the case of the nasal tumors in rats, tumors occurred at higher doses of alachlor (42 and 126 mg/kg/day), and in a second study, nasal tumors were observed at 15 mg/kg/day. A single nasal tumor observed in female rats at 2.5 mg/kg/day was considered noteworthy by the CPRC, as it is considered a rare tumor type. Data submitted to the Office of Pesticide Programs subsequent to the carcinogenicity studies in rats demonstrated that the diethylbenzoquinone imine metabolite of alachlor was involved in nasal tumor production. Based on the reactive nature of this metabolite, studies were conducted to investigate potential protein and/or DNA binding from alachlor administration. In an *in vivo/in vitro* unscheduled DNA synthesis study in rats, alachlor showed a weak UDS response at 1000 mg/kg/day, a dose approximating the median lethal dose in rats. In a protein binding study, radiolabeled alachlor was fed to female Long-Evans rats at 126 mg/kg/day for 13 days. Results showed a direct correlation between binding to nasal proteins and length of treatment. The major adduct was identified as the 3,5-diethylbenzoquinone-4-imine-cysteine adduct. The protein adduct formation at doses causing significant production of nasal tumors in rats is consistent with the proposed non-linear mode of action for alachlor, involving cytotoxicity with a compensatory increase in cell turnover and eventual production of tumors. It is recognized by both OPP and

the registrant that rats and humans possess a similar mechanism for formation of the diethylbenzoquinone imine metabolite, and it is also recognized that large quantitative differences exist between rats and humans for formation of this metabolite (see above discussion under human data). For these reasons, the CPRC agreed with the SAP that the nasal response is best characterized by a non-linear mode of action (MOE) approach to human risk assessment of alachlor. The SAP also concluded that the nasal tumors are the endpoint most appropriate for a cancer risk assessment, since they occurred at doses below those considered excessive.

The mechanism of induction of glandular stomach tumors has also been investigated by the registrant and the data reviewed by the OPP. It has been shown that the gastric tumors from alachlor administration involve toxicity to the fundic mucosa with subsequent loss of parietal cells. The mucosal atrophy leads to compensatory cell proliferation in the fundic mucosa, while loss of parietal cells results in hypochlorhydria. The resulting increase in gastric pH induces excessive production of gastrin. The trophic effect of gastrin further drives a sustained proliferative response with ultimate induction of gastric neoplasms. The CPRC concluded that this mode of action is best characterized by a non-linear approach. The SAP concluded that since the statistically significant increase in stomach tumors was seen only at the highest dose tested (126 mg/kg/day), a dose the Panel felt was excessive for assessing carcinogenicity, these tumors are probably not relevant to humans. However, the CPRC agreed that since these are rare tumors, the single tumor observed at the next lowest dose (42 mg/kg/day), which is not considered an excessive dose, was noteworthy.

For the thyroid follicular cell tumors, data have been developed by the registrant and reviewed by OPP which show that the follicular cell tumors induced by alachlor at 126 mg/kg/day are the result of induction of hepatic uridine 5'-diphosphoglucuronyl transferase by repeated oral alachlor administration, with a subsequent fall in circulating thyroxine and triiodothyronine, elevation of circulating thyroid stimulating hormone, and production of hyperplasia and neoplasia of the thyroid through continual stimulation of the thyroid by TSH. These data have also been published by the registrant (Fund. Appl. Toxicol. 33: 16-23, 1996) and are consistent with the Agency's position on chemicals which induce thyroid neoplasia through this mechanism. The SAP concluded that while these tumors may be relevant for humans, their usefulness for risk assessment is questioned since the tumors occurred only at the top dose which the SAP considered excessive for assessment of carcinogenicity.

E. Other Data

1. Mutagenicity and Cell Proliferation

Alachlor has been tested in a variety of assays examining mutagenic/genotoxic potential. Alachlor itself and many of its metabolites have generally been negative in the Salmonella assay for gene mutations, including using microsomes from uninduced rat, mouse or monkey nasal turbinates. However, a few metabolites of alachlor, including a key intermediate to the ultimate benzoquinone imine metabolite, i.e. 2,6-diethylaniline, have demonstrated some activity, albeit mostly weak, in the Salmonella assay. Alachlor has also demonstrated DNA damaging capability as indirectly shown by unscheduled DNA synthesis (UDS) activity in rat livers after an *in vivo* exposure to 1000 mg/kg. The clastogenicity of alachlor has been demonstrated *in vitro* from several published studies, including cytogenetic studies from animal and human cells with aberration and single-cell gel electrophoresis analyses (e.g., Toxicol 104: 129-140, 1995; Mutagenesis 10: 417-423, 1995; Mutat Res 344: 41-54, 1995). However, most *in vivo* studies, with few exceptions, for aberration and micronuclei induction are generally negative at doses up to 1000 mg/kg.

Female Long-Evans rats given a 123 mg/kg radiolabelled oral dose of alachlor demonstrated nasal tissue DNA binding after 24 hours. Qualitatively, a low level binding to nasal DNA was found, but could not be quantitated. A much higher level of protein binding in both liver and nasal turbinate tissues was observed. This suggests that metabolite(s) of alachlor bind to macromolecules such as protein and DNA, and while protein binding is preferential at doses not considered excessive, both may contribute to the etiology of nasal tumors.

Alachlor caused a sustained cell proliferative effect at a dose of 252 mg/kg/day in the olfactory epithelium of the nasal turbinates of rats, but not mice (260 mg/kg/day) when fed alachlor at these dose levels for up to 60 days. Additionally, alachlor was found to significantly induce stress genes (e.g., nmo and hsp70) in olfactory epithelia after a 60 day exposure to rats at 126 mg/kg/day of alachlor - this suggests the nasal turbinate cells are under physiological stress from alachlor exposure. These results are consistent with the production of nasal tumors at these dose levels.

The data on mutagenicity as a whole suggest that genotoxic species of alachlor may be produced. However, it is proposed that genotoxic activity and cell proliferation are observed at doses of alachlor in which GSH depletion and/or saturation of protein

binding has occurred. Therefore, the possible genotoxic activity of alachlor may not manifest itself at doses where moieties such as GSH are not depleted. These data are supportive of a nonlinear mode of action for tumor induction.

2. Structure-Activity Relationships

Several structurally related chloroacetanilide and other compounds have been shown to induce tumors at one or more of the same sites as alachlor. Statistically significant increases in nasal tumors have been reported for acetochlor and butachlor in rats. Nasal tumors (1 adenocarcinoma and 1 fibrosarcoma) have also been reported in rats fed metolachlor at 3000 ppm in the diet; however, the results did not reach statistical significance. But overall, nasal turbinate tumors are considered to be rare and these results are supportive of a neoplastic response at that site by these compounds.

Stomach tumors have been reported for acetochlor and butachlor in rats. Male Sprague-Dawley rats administered dimethenamid in the diet for 104 weeks showed trend and pairwise statistically significant epithelial hyperplasia of the stomach. Stomach lesions have been reported in CD-1 mice of both sexes administered propachlor in the diet for 18 months at levels of 0, 100, 500, 1500 or 6000 ppm. Herniated mucosal glands into the submucosa/tunica muscularis were observed in both sexes at the highest dose and in some males at the next highest dose level. Males at the highest dose level also showed erosion/ulceration of the glandular mucosa of the stomach.

Thyroid follicular cell tumors have been reported for acetochlor and butachlor in rats. Additionally, in Sprague-Dawley rats tested with propachlor at doses of up to 500 ppm in the diet for 104 weeks, the incidence of thyroid neoplasia appeared to be increased, but remain within historical control levels.

These data support the evidence that these three tumor types are related to exposure to these related compounds, including alachlor.

F. Weight of the Evidence

The weight of evidence is based on: a) tumors of the nasal epithelium, stomach, and thyroid observed at higher doses in rats; b) the species sensitivity of the response; and c) the evidence for a nonlinear mode of action for tumor induction at each site.

The CPRC recognizes that while the response occurs only at higher doses and quantitative differences exist in sensitivity between rats and humans, a similar mechanism for nasal tumor production is present in humans, and therefore its relevance to humans cannot be dismissed. The SAP agrees with this position. The rarity of the nasal tumor type and SAR support also adds to the CPRC's concern. The presence of stomach tumors, which are also considered a rare tumor type, and the lack of a consistent histopathologic response, leads to the conclusion that some hazard potential may exist in humans after intense exposures. Clarification of the similarity or dissimilarity of the relevance of the rat stomach tumors could shed light on this uncertainty. The CPRC agrees that the rat stomach tumors are relevant to humans at this time. The CPRC agrees with the SAP in that thyroid tumor induction may be relevant to humans, but that the tumors in rats were seen at an excessive dose.

Based on the weight of the evidence presented to the CPRC, the Committee agrees that a nonlinear risk assessment be applied to the alachlor cancer data. Since the two tumor types of major concern are the nasal and stomach tumors, a margin of exposure (MOE) approach is recommended for both. Since these are considered rare tumor types, **for purposes of risk assessment, the MOE for the nasal tumors should be determined with 0.5 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level. Also, the MOE for the stomach tumors should be determined with 14 mg/kg/day as the "point of departure" as no tumor response was seen at this dose level.** Both tumor types were present at the next highest tested dose level (females at 2.5 mg/kg/day in the 1983 rat study for nasal tumors; females at 42 mg/kg/day in the 1981 rat study for stomach tumors). While not statistically significant at these next higher dose levels, the Committee considered tumor presence biologically significant due to their rarity in rats.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the *EPA proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996)* for classifying the weight of evidence for alachlor.

In accordance with these EPA proposed Guidelines, the CPRC unanimously agreed to characterize the weight of the evidence for alachlor as "likely" at high doses but "not likely" at low doses to be a human carcinogen by all routes of exposure. This conclusion was based on increased incidences of malignant and combined benign/malignant multiple tumor types in both sexes of the Long Evans rat, which occurred mainly at higher doses. Mechanistic considerations were also included in this decision process and data from structural analogs and genotoxicity provided additional support.

The CPRC agreed that a non-linear approach (MOE) should be used for the purpose of risk assessment. The consensus of the CPRC was that MOEs for both the malignant mixed gastric tumors and the nasal adenomas be included in a risk assessment that presents a range of MOEs based on tumor induction.